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Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection

Intravenous viruses are used to target deadly bacterium; dramatic case suggests potential alternative to failin

April 25, 2017 | Scott LaFee and Heather Buschman, PhD

Scientists and physicians at University of California San Diego School of Medicine, working with colleagues at the U.S. Navy Medical Research Center – Biological Defense (NMRC-BDRD), Texas A&M University, a San Diego-based biotech and elsewhere, have successfully used an experimental therapy involving bacteriophages — viruses tha specific strains of bacteria — to treat a patient near death from a multidrug-resistant bacterium.

Phage Therapy

Phage Therapy Infected with a multidrug-resistant bacterium, Tom Patterson was comatose and near-death. Physicians and scientists at UC San Diego Health, with many coll experimental bacteriophage therapy — viruses that target and consume bacteria — to save his life. The success may be a catalyst to developing new remedies to the growing ; antimicrobial resistance.

The therapeutic approach, which has been submitted to a peer-reviewed journal, is scheduled to be featured in an oral presentation tomorrow at the Centennial Celebration of at the Institute Pasteur in Paris by Biswajit Biswas, MD, one of the case study’s co-authors and chief of the phage division in the Department Genomics and Bioinformatics at is Human Phage Therapy Day, designated to mark 100 years of clinical research launched by Felix d’Herelle, a French-Canadian microbiologist at Institute Pasteur who is cr bacteriophages with British bacteriologist Frederick Twort.

Authors say the case study could be another catalyst to developing new remedies to the growing global threat of antimicrobial resistance, which the World Health Organizatic

least 50 million people per year by 2050. Based on the success of this case, in collaboration with NMRC, UC San Diego is exploring options for a new center to advance research in bacteriophage-based therapies.

“When it became clear that every antibiotic had failed, that Tom could die, we sought an emergency investigational new drug application from the FDA to try bacteriophages. [“Chip” Schooley, MD](#), professor of medicine, chief of the Division of Infectious Diseases in the UC San Diego School of Medicine and primary physician on the case.

“To our knowledge, he is the first patient in the United States with an overwhelming, systemic infection to be treated with this approach using intravenous bacteriophages. From death, he’s recovered well enough to go back to work. Of course, this is just one patient, one case. We don’t yet fully understand the potential — and limitations — of clinical phage therapy, but it’s an unprecedented and remarkable story, and given the global health threat of multidrug-resistant organisms, one that we should pursue.”



Bacteriophages (green) attacking a bacterium (orange). Image courtesy of Graham Beards.

Infection on vacation

The story begins in late-2015. Tom Patterson, PhD, a 69-year-old professor in the Department of Psychiatry at UC San Diego School of Medicine, and his wife, Steffanie Strathdee, MD, a professor in the Division of Global Public Health in the Department of Medicine, were spending the Thanksgiving holiday in Egypt when Patterson became ill, wracked by abdominal pain, fever, and a racing heartbeat. Local doctors diagnosed pancreatitis — inflammation of the pancreas — but standard treatment didn’t help.

Patterson’s condition worsened and he was medevacked to Frankfurt, Germany Dec. 3, 2015, where doctors discovered a pancreatic pseudocyst, a collection of fluid around the pancreas that was drained and the contents cultured. Patterson had become infected with a multidrug-resistant strain of *Acinetobacter baumannii*, an opportunistic and often deadly pathogen that proved particularly problematic in hospital settings and in the Middle East, with many injured veterans and soldiers returning to the U.S. with persistent infections.

Initially, the only antibiotics with any effect proved to be a combination of meropenem, tigecycline and colistin, a drug of last resort because it often causes kidney damage, but Patterson’s condition stabilized sufficiently for him to be airlifted Dec. 12, 2015, from Germany to the Intensive Care Unit (ICU) at Thornton Hospital at UC San Diego Health. There, doctors discovered that his bacterial isolate had become resistant to all of these antibiotics.

At Thornton Hospital, now part of Jacobs Medical Center, Patterson began to recover, moving from the ICU to a regular ward. But the day before scheduled discharge to a local hospital, an internal drain designed to localize his infection and keep it at bay slipped, spilling bacteria into his abdomen and bloodstream. Patterson immediately experienced severe abdominal pain and began racing. He could not breathe. He became feverish and would subsequently fall into a coma that would last for most of the next two months. He was, in effect, dying.

“That’s a period of my life I don’t remember,” recalled Patterson. “There was so much pain that it’s almost beyond your ability to cope. I’m happy not to remember.”

Strathdee, his wife, is no stranger to the terrors of disease. As an infectious disease epidemiologist and director of the UC San Diego Global Health Institute, she has worked in India to Afghanistan to Mexico, trying to lower HIV infection and mortality rates.

“There came a point when he was getting weaker and weaker, and I didn’t want to lose him. I wasn’t ready to let him go and so I held his hand and said, ‘Honey, they’re doing everything there’s nothing that can kill this bug, so if you want to fight, you need to fight. Do you want me to find some alternative therapies? We can leave no stone unturned.’”

Tom recalled the moment: “I vaguely remember you saying, ‘do you want me to try or not because it’s going to be a tough time and it’s not certain that it will work.’ I remember it but it was just a flash in the whole process.”

Strathdee began doing research. A colleague mentioned a friend had traveled to Tbilisi, Georgia to undergo “phage therapy” for a difficult condition and had been “miraculously cured.” She learned of bacteriophages while she was a student, but they were not part of mainstream medical doctrine. She turned to strangers in the phage research community and to her husband for help.

Bacteriophages are ubiquitous viruses, found wherever bacteria exist. It’s estimated there are more than 10^{31} bacteriophages on the planet. That’s ten million trillion trillion, more than any other organism on Earth, including bacteria, combined. Each is evolved to infect a specific bacterial host in order to replicate — without affecting other cells in an organism.

The idea of using them therapeutically is not new. Described a century ago, phage therapy was popular in the 1920s and 1930s to treat multiple types of infections and conditions. However, it was inconsistent and lacked scientific validation. The emergence of antibiotics in the 1940s pushed phage therapy aside, except in parts of Eastern Europe and the former Soviet Union, where it remained a topic of active research.

With dwindling options, Strathdee, Schooley and colleagues went looking for help. They found many researchers willing to help. Three teams possessed suitable phages that could treat Patterson’s particular bacterial infection: the Biological Defense Research Directorate of the NMRC in Frederick, MD; the Center for Phage Technology at Texas A&M University; and a San Diego-based biotech company specializing in bacteriophage-based therapies. A research team at San Diego State University, headed by microbial ecologist Forest Rowley, provided phage samples for clinical use.

With emergency approval from the Food and Drug Administration, each source provided phage strains to UC San Diego doctors to treat Patterson, with no guarantee that any would actually work. “That’s one of the remarkable things to come out of this whole experience,” said Schooley, “the incredible and rapid collaboration among folks scattered around the world during a desperate time and people really stepped up.”

Phage therapy is typically administered topically or orally. In Patterson’s case, the phages were introduced through catheters into his abdominal cavity and intravenously to treat the infection, which had not been done in the antibiotic era in the U.S. “That makes them more effective,” said Schooley. “The action is at the interface of the patient and the organism.”

With tweaking and adjustments — his physicians were learning on the fly — Patterson began to improve. He emerged from his coma within three days of the start of IV phage therapy, turned to his daughter and said, ‘I love you’,” recalled Schooley. Patterson was soon weaned off of the respirator and blood pressure drugs.



Robert “Chip” Schooley, MD, professor of medicine and chief of the Division of Infectious Diseases in the UC San Diego School of Medicine.

“As a treating doctor, it was a challenge,” said Schooley. “Usually you know what the dosage should be, how often to treat. Improving vital signs is a good way to know that you’re on the right track, but when you’re doing it for the first time, you don’t have anything to compare it to.”

“A lot was really worked out as we went along, combining previous literature, our own intuition about how these phages would circulate and work and advice from people who had used phage therapy about this for a long time.”

Treatment details

By the time Patterson was airlifted to Thornton Hospital at UC San Diego Health, he was in dire straits. His abdomen had swelled, distended by the pseudocyst teeming with bacteria.

baumannii. His white blood cell count had soared — a sign of rampant infection.

Doctors tried various combinations of antibiotics. He developed respiratory failure and hypotension that required ventilation and recurrent emergency treatment. He became ill. When he lapsed into a coma in mid-January, he was essentially being kept alive on life support. Eventually Schooley said there were no antimicrobial agents left to try. Strath was wondering aloud if she was prepared for Tom to die.

She wasn't. Bacteriophage therapy began March 15, 2016, with a cocktail of four phages provided by Texas A&M and the San Diego-based biotech company AmpliPhi, pumped into the pseudocyst. If the treatment didn't kill him, Patterson's medical team planned to inject the Navy's phages intravenously, flooding his bloodstream to reach the infected body. As far as Patterson's doctors knew, such treatment had never been tried before.

On March 17, the Navy phages were injected intravenously. There were fears about endotoxins naturally produced by the phages. No one knew what to expect, but Patterson was well — indeed there were no adverse side effects — and on March 19, he suddenly awoke and recognized his daughter.

"One of NMRC's goals with respect to bacteriophage science has been providing military members infected with multidrug-resistant organisms additional antimicrobial options experienced and well-positioned to provide an effective phage cocktail for Dr. Patterson," said Theron Hamilton, PhD, head of Genomics and Bioinformatics at the Navy's Biomedical Research Directorate. "Obviously, we are thrilled with the outcome and hope this case increases awareness of the possibility of applying phage therapy to tough cases like this."

Subsequent treatment, however, would not be easy. The learning curve was steep and unmarked. There were bouts of sepsis — a life-threatening complication caused by massive improvement, Patterson's condition remained precarious. Doctors discovered that the bacterium eventually developed resistance to the phages, what Schooley would characterize as a "Darwinian dance," but the team compensated by continually tweaking treatment with new phage strains — some that the NMRC had derived from sewage — and antibiotics.

In early May, Patterson was taken off of antibiotics. After June 6, there was no evidence of *A. baumannii* in his body. He was discharged home August 12, 2016.

Post-treatment and beyond

Recovery has not been entirely smooth and steady. There have been setbacks unrelated to the phages. A formerly robust man, Patterson had been fed intravenously for months, lost 100 pounds, much of it muscle. He has required intense physical rehabilitation to regain strength and movement. "It's not like in the movies where you just wake up from pop out of bed," Patterson said. "You discover that your body doesn't work right anymore." He said he could feel parts of his brain coming back alive.

Steffanie Strathdee, PhD, and Tom Patterson, PhD at home.

Nonetheless, Patterson described the experience as miraculous. Even comatose, when he often wrestled with imagined demons, he recalled hearing and recognizing voices and his darkness, there was life and hope.

And beyond him, he hopes his experience will translate into new treatments for others: "The phage therapy has really been a miracle for me, and for what it might mean that it may be cured from multidrug-resistant infections in the future. It's been sort of a privilege."

Schooley said Patterson was lucky. His wife was a trained scientist and determined to find a remedy — and they both worked at UC San Diego School of Medicine: "He was that had all of the resources and courage necessary to support him while this innovative therapy was developed, which was essentially a home brew cocktail of viruses to be given individual. I think a lot of other places would have hesitated. I think the response that he had clinically has been very gratifying and speaks to the strength of a multidimensional of the pieces you need."

Still, Schooley said any broad, future approved application of phage therapy faces fundamental challenges unlike past treatments. "What the FDA is used to saying is 'This is what its structure is and how you can give it to multiple people.' With bacteriophage therapy, the FDA would be dealing with an approach in which doctors would have to develop each patient tailored to their infecting organisms. It's the ultimate personalized medicine."

The good news, Schooley said, is that new molecular tools, robotics and other advances make personalized medicine possible in a way it wasn't 10 or 15 years ago. "Then, it impossible to contemplate. There's still much research to be done, but I think there are going to be a lot of clinical applications where this approach may be very beneficial to

More about bacteriophages

Derived from the Greek words meaning "bacteria eater," bacteriophages are ancient and abundant — found on land, in water, within any form of life harboring their target. A San Diego State University and colleagues in their book *Life in Our Phage World*, phages cause a trillion trillion successful infections per second and destroy up to 40 percent of the ocean every day.

Thousands of varieties of phage exist, each evolved to infect only one type or a few types of bacteria. Like other viruses, they cannot replicate by themselves, but must command machinery of bacteria. To do so, they attach to a bacterium and insert their genetic material. Lytic phages then destroy the cell, splitting it open to release new viral particles to such, phages could be considered the only "drug" capable of multiplying; when their job is done, they are excreted by the body.

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